Title: INTER-HEART
Topic: Prevention/Vascular
Interviewee: Salim Yusuf, MD, FACC
Interviewer: Peter Sleight, MD, FACC

The Challenge:
Once considered a "Western" problem, cardiovascular disease is now a major global problem. Economic development brings higher wages and a Western lifestyle, including more tobacco smoking; a lack of physical activity; and a diet high in fat, sugar, and salt – all widely recognized as contributing factors to the development of coronary heart disease (CHD). Consequently, the U.S. National Academy of Sciences estimates that CHD became the developing world's leading cause of death in the mid-1990s. The World Health Organization (WHO) projects it hasn't quite happened yet, but will by 2010. Either way – and despite the fact that cardiovascular mortality has declined in most developed countries – cardiovascular disease is now the leading cause of global morbidity and mortality.

To promote interventions that can curb the worldwide spread of CHD, more data are needed to assess relevant risk factors in various regions, quantify the impact of each risk factor alone and in combination on population risk, and determine important differences in each region, each ethnic group, in both men and women, and in both the young and old.

Current thinking suggests that only about half of CHD is accounted for by known risk factors. However, new data suggest that this estimate is wildly inaccurate.

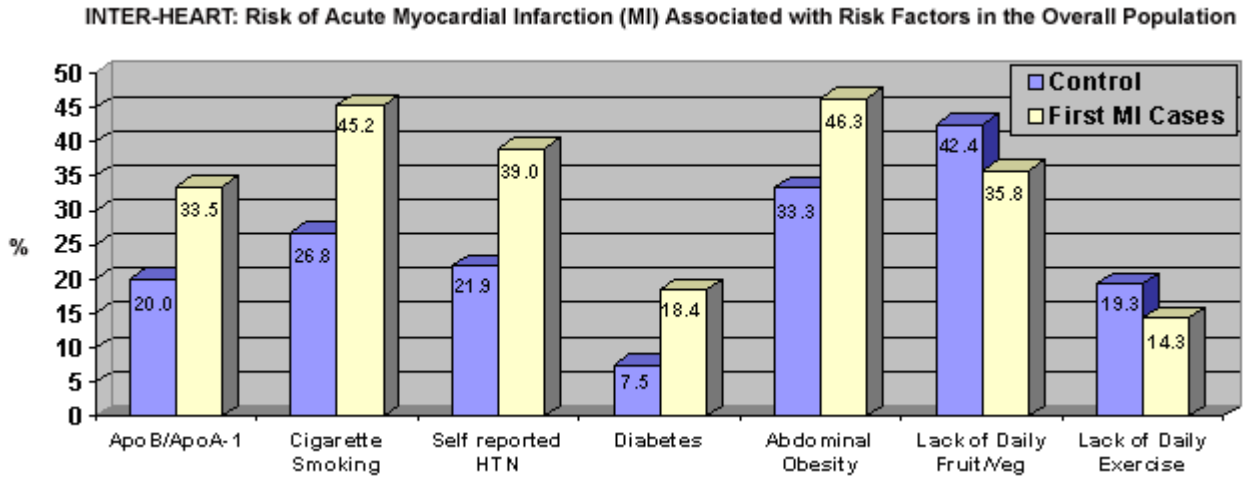
The Data:
Despite the fact that 80% of the world's CHD burden is now spread across low- and medium-income countries, Salim Yusuf, MD, FACC, said "We had practically no data in these countries. So, we thought it was time to do a proper study."

That study became the INTER-HEART trial, one of the largest case-controlled studies to examine the risk factors for acute myocardial infarction (AMI).[1, 2, 3] Investigators in 52 countries (including the United States and Canada) gathered data to assess the relative importance of both traditional and emerging risk factors across these populations. The study included 15,152 incident cases of AMI and 14,820 age- and sex-matched controls with no history of heart disease.

Sponsored by the WHO and the World Heart Federation, the INTER-HEART results suggest that risk factors are more alike worldwide than ever imagined.[4] Nine easily measurable risk factors predicted 91% of the global risk of AMI (Slide 1). Of these risk factors, the two most important turned out to be an abnormal ratio of apolipoprotein B (Apo-B)/Apo-A-1 and smoking (Slide 2).

Dr. Yusuf, the principal investigator for INTER-HEART, admitted that the results surprised him because he expected to see major differences in risk factors based on geography and ethnicity. “But in the end, we found risk factors behaved the same way and had the same impact in every ethnic group, in every region, in men and women, and – contrary to what we expected – was even more strongly apparent in young people.”

Another major finding: Risk of AMI increased significantly with even minimal smoking or dyslipidemia. For example, he said, “If you even smoke two or three cigarettes a day, your risk of AMI increases 40%.” A linear relationship was apparent; 10 cigarettes per day was associated with a two-fold increased risk of AMI, 20 cigarettes per day led to a four-fold increased risk, and smoking 40 cigarettes per day produced an eight- or nine-fold increased risk.



Investigators looked at family history, too. While family history was associated with about a one-and-a-half-fold excess risk of AMI, overall it added little to the leading risk factors. “With these nine risk factors we were able to predict about 91% of the global risk,” said Dr. Yusuf. “When you add family history, it goes to 92%.” What that means, he added, is that a large part of family history is shared lifestyles and, perhaps, shared genes. “However, these are probably genes related to the risk factors we measured, such as obesity or abnormal lipids.”

Interpretation:
There are important implications to the INTER-HEART findings. From a practical perspective, Dr. Yusuf said, “We know enough today that if we implement available interventions fully, we should be able to prevent the majority of premature heart disease in the world. Second, the data provide a basis for a global strategy for CHD prevention that utilizes similar principles in various regions of the world, taking into account local economic and cultural factors. Finally, future research is likely to be particularly fruitful if focused on why known risk factors develop and how they can be substantially modified.

“The practical implications are political really,” he said. “We have to introduce social engineering to make people exercise more, smoke less, and maintain the social structure because there was an important psychosocial aspect to this study.” Specifically, life stress events, such as depression, anger, hostility, and little control over daily work, all independently pointed in the same direction: stressful events collectively increase (AMI) risk by about two-and-a-half-fold. For a given population, he said, about 30% of AMI risk included psychosocial stressors, about half could be attributed to an abnormal lipid ratio, and about 30% of AMI events had a smoking component.

What are the implications of the INTER-HEART data in terms of the importance of putative risk factors, such as prothrombotic factors (fibrinogen, PAI-1), inflammatory markers, and elevated levels of homocysteine? Said Dr. Yusuf, “These markers probably have a much smaller role (in AMI risk) than the standard markers. I don't think there is another risk factor as important as the lipids, smoking, diabetes, or hypertension.”

Second Opinion:
This is an important study with immediate implications wherever you live. The INTER-HEART findings will be relevant

for developing health policies that can be applied to different countries and ethnic groups. Importantly, the study may also lead to cohort studies in participating nations and foster a network of committed investigators in more than 50 countries.

References

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2. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation* 2001;104:2746-53.

3. Yusuf S, Reddy S, Ounpuu S, Anand S Global burden of cardiovascular diseases: Part II: variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies. *Circulation* 2001;104:2855-64.

4. In press *Lancet* 2004;:-